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10/698,121	10/31/2003	Dominic Cosgrove	249.0007 0101	8958

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EXAMINER

HADDAD, MAHER M

ART UNIT PAPER NUMBER

1644

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/698,121		COSGROVE, DOMINIC	
	Examiner		Art Unit	
	Maher M. Haddad		1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
- 4a) Of the above claim(s) 4,9,14,16,20,24 and 26-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-8,10-13,15,17-19,21-23 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/04&4/05</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1644

DETAILED ACTION

1. Claims 1-42 are pending.
2. Applicant's election with traverse of Group II, claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 drawn to a method of treating a patient having a chronic inflammatory disease with a blocking agent wherein the blocking agent is a neutralizing antibody and renal fibrosis as the species filed on 1/10/06, is acknowledged.

Upon reconsideration, the Examiner has extended the search to cover crescentic glomerulonephritis species.

Applicant comments regarding claims 3 and 11 are to be included in the listing of linking claims, as both are drawn to a method comprising administering an agent. Further Applicant comments that the linking claims does not only link the inventions of Group I and II but also link the invention of Group III was not found convincing. Claims 3 and 11 recite Markush group listing the chronic inflammatory disease species. Such a species are not a genus claim, and therefore do not link any invention. Further, the claims in Group III are independent claims and do not depend from any of the linking claims. Therefore, the restriction requirement is proper.

Applicant's traversal is on the grounds that the inventions as claimed can be readily evaluated in one search without placing undue burden on the Examiner. That is, all the claims are so interrelated that a search of one group of claims will reveal art to the others. Applicant further submits that searching Group I and Groups II together would not pose undue burden on the Examiner. Further Applicant submits that by restricting the claimed invention into VII Groups would require substantial duplication of work on the part of the U.S. Patent Office. This is not found persuasive because the specific antibodies/peptides are recognized divergent subject matter. In addition, the antibodies and peptides are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Therefore the methods of treating a chronic inflammatory disease with a blocking agent wherein the blocking agent is specific antibodies/peptides are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4, 9, 14, 16, 20, 24 and 26-42 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 drawn to a method of treating a patient having a chronic inflammatory disease with a blocking agent wherein the blocking agent is a neutralizing antibody and renal fibrosis and crescentic glomerulonephritis as the species.

Art Unit: 1644

5. Applicant's IDS, filed 8/23/04 and 4/18/05, is acknowledged.

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 16, line 32 to page 11, line 7 contains embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

7. Claim 7 is objected to because the word "distrupts" is misspelled. Correction is required.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 17-20, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 17 and 22 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step with the reagents necessary for the method recited.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating renal fibrosis or crescentic glomerulonephritis in patient comprising administering to the patient an anti- $\alpha 1\beta 1$ integrin receptor antibody does not reasonably provide enablement for a method of treating a patient having any "chronic inflammatory disease", the method comprising administering to the patient any "blocking agent" to neutralize the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin in claim 1, wherein the chronic inflammatory disease is characterized by progressive pathogenesis resulting from infiltrating monocytes, lymphocytes, or both in claim 2, wherein the chronic inflammatory disease is renal fibrosis or crescentic glomerulonephritis in claim 3, wherein the blocking agent is any "neutralizing antibody" in claim 6, or a method for treating a subject having any "inflammatory disease or other condition" where integrin $\alpha 1\beta 1$ -positive interstitial monocyte and/or lymphocyte accumulating is observed, the method comprising

Art Unit: 1644

administering to the subject any “active agent” that disrupts the interaction between Collagent XIII and $\alpha 1\beta 1$ integrin in claim 7, wherein the active agent blocks binding of Collagen XIII and $\alpha 1\beta 1$ integrin in claim 8, wherein the blocking agent is any “antibody” in claim 10, wherein the inflammatory disease or other condition is renal fibrosis or crescentic glomerulonephritis in claim 11, wherein the active agent blocks the integrin of $\alpha 1\beta 1$ integrin on peripheral blood monocytes and/or lymphocytes with Collagen XIII on vascular endothelium of chronically inflamed tissues in claim 12, or a method of reducing selective efflux of integrin $\alpha 1\beta 1$ -positive monocytes into the interstitium of chronically inflamed tissues, the method comprising contacting the $\alpha 1\beta 1$ integrin on peripheral blood monocytes and/or lymphocytes with any “active agent” that interferes with the interaction between Collagen XIII and $\alpha 1\beta 1$ integrin in claim 13, wherein reducing selective efflux of integrin $\alpha 1\beta 1$ -positive monocytes into the interstitium of chronically inflamed tissues comprises contacting an antibody that binds to the Collagen XIII ligand on the cell surface of the vascular/capillary endothelial cells of inflamed tissues under conditions effective to block the binding site for Collagen XIII in claim 15, or a method of reducing the rate of monocyte and/or lymphocyte efflux into the interstitial space of chronically inflamed tissues, the method comprising blocking Collagent XIII from binding with $\alpha 1\beta 1$ integrin in claim 17, wherein the blocking comprises blocking the Collagen XIII ligand in clai 18, wherein the blocking comprises blocking Also, at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant’s specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success in claim 19, wherein blocking comprises contacting the Collagen XIII ligand with a mono-specific antibody in claim 21, or a method of reducing the rate of monocyte and/or lymphocyte efflux into interstitial space of chronically inflamed tissues, the method comprising blocking Collagen XIII from binding with $\alpha 1\beta 1$ integrin in claim 22, or a method of blocking the interaction of $\alpha 1\beta 1$ integrin on peripheral blood monocytes and/or lymphocytes with Collagen XIII on vascular endothelium of chronically inflamed tissues, the method comprising contacting the monocytes and/or lymphocytes, the vascular endothelium, or both with any “agent” that either occupies the Collagen XIII binding site on $\alpha 1\beta 1$ integrn or blocks the $\alpha 1\beta 1$ binding site on Collagen XIII in claim 23 wherein the agent that blocks the $\alpha 1\beta 1$ binding site on Collagen is a neutralizing monoclonal antibody in claim 25The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification does not reasonably provide enablement for a method for treating any “inflammation” including chronic, comprising delivering to the tissue **any blocking/active agent** that “neutralize the capacity of Collagen XIII to bind to the $\alpha 1\beta 1$ integrin”. The specification does not enable any person skilled in the art to which it pertains, or with which it is

Art Unit: 1644

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification on page 23, lines 19-21, discloses that interaction of $\alpha 1\beta 1$ integrin on monocytes mediates transmigration into the interstitial space in chronic inflammatory diseases. The specification further discloses that identification of the endothelial cell-specific ligand may provide a therapeutic target of significant importance. Blocking the ligand with a neutralizing antibody or peptide inhibitor might be applied alone or in combination with blocking $\alpha 1\beta 1$ integrin on the peripheral blood monocytes. This strategy will have implications for other chronic inflammation diseases (see page 23, lines 23-28). While it is well known that hallmark of chronic inflammation is mononuclear cells: T cells, plasma cells, monocytes as opposed to acute inflammation, where the hallmark is neutrophils, the specification only discloses an observation that the monocytes in the Alport tubulointerstitium were predominantly positive for $\alpha 1\beta 1$ integrin. The specification concludes on page 33, lines 25-30, that this observation may reflect recruitment of $\alpha 1\beta 1$ integrin-positive monocytes from the peripheral blood, or activation of $\alpha 1\beta 1$ integrin expression in monocytes following entry into the tubulointerstitial space. However, on the basis of the disclosed apparent in vitro observation alone, applicant concludes that the scope of the anti- $\alpha 1\beta 1$ integrin antibody can have biological activity to inhibit the adhesion of infiltrating monocytes, lymphocytes, or both and be provided as pharmaceutical compositions to subjects including human to effectively inhibit the binding of collagen XIII to $\alpha 1\beta 1$ integrin. While proteins that interact with integrin cytoplasmic domains have been identified, however the role of these interactions in integrin signaling is still uncertain. Further, due to the unique nature of brain endothelial cells for example, the unpredictability of leukocyte/endothelial receptor interaction, little is known about the different types of adhesion molecules expressed on brain endothelial cells during brain inflammation, and little has been accomplished to ameliorate the effects of chronic inflammatory brain diseases, such as MS using the claimed antibody to $\alpha 1\beta 1$ integrin.

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. MPEP § 2164.03.

The specification discloses that a blocking agent (e.g., a peptide or a neutralizing antibody) to neutralize the capacity of Collagen XIII to bind the $\alpha 1\beta 1$ integrin (see page 2, lines 17-18). The specification on page 4, lines 19-21, discloses that the "agent" is an antibody that blocks the interaction of Alexa-conjugated purified $\alpha 1\beta 1$ integrin to MCP-1 treated vascular endothelial cells in culture. The specification on page 10, lines 13-15 discloses that the present invention also provides methods of identifying agents (e.g., small organic molecules, peptides, antibodies, SiRNAs) suitable for use in such therapeutic methods. The specification does not provide a sufficient enabling description of the claimed agents. The term "agent" as recited encompass any agent that neutralize the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin. It was well

Art Unit: 1644

known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "agonists" and "antagonists". However, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Further, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictability was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any agent such as a simple or complex organic or inorganic molecule, a peptide, a protein (e.g. antibody) or an oligonucleotide (e.g. anti-sense) are fraught with uncertainties.

While "agent" of that that neutralize the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin may have some notion of the function of the claimed molecules; there is insufficient biochemical or structural information to enable the skilled artisan to make and use any "agent" as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Given the unpredictability associated with identifying individual molecules which would function to neutralized the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Art Unit: 1644

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/61040, as is evidence by Dominic Cosgrove Declaration filed in serial No. 10/099,573 on 11/29/04.

The WO '040 publication teaches and claims a of treating renal fibrosis or crescentic glomerulonephritis (chronic inflammatory diseases), in a patient comprising administering to the patient an effective amount of an $\alpha 1\beta 1$ integrin receptor inhibitor (a blocking agent) (see published claims 1 and 12-13 in particular), wherein the $\alpha 1\beta 1$ integrin receptor inhibitor is a blocking agent that binds to the $\alpha 1\beta 1$ integrin receptor binding site on the surface of a kidney cell (see published claim 8, in particular), wherein the agent is an antibody (see published claim 11 and Example 5 on page 53 in particular).

While the prior art teachings may be silent as to the "to neutralize the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin", "characterized by progressive pathogenesis resulting from infiltrating monocytes, lymphocytes, or both", "the blocking agent blocks the interaction of $\alpha 1\beta 1$ integrin on peripheral blood monocytes and/or lymphocytes with collagen XIII on vascular endothelium of chronically inflamed tissue", "where integrin $\alpha 1\beta 1$ -positive interstitial monocyte and/or lymphocyte accumulation is observed", "reducing selective efflux of integrin $\alpha 1\beta 1$ -positive monocytes into the interstitium of chronically inflamed tissues" or reducing the rate of monocyte and/or lymphocyte efflux into the interstitial space of chronically inflamed tissues" per se; the method, the product used in the reference method are the same as the claimed method. Therefore mechanism driving the process of inflammation is considered inherent properties of the referenced method.

Further, as is evidence by Dominic Cosgrove Declaration filed in serial No. 10/099,573 on 11/29/04 that the work describes the existence of an inducible ligand (collagen XIII) for $\alpha 1\beta 1$ integrin on the vascular endothelial cells of inflamed tissue (in this case, the inflamed kidney) that binds to $\alpha 1\beta 1$ integrin-positive peripheral blood monocytes and mediates the transmigration

Art Unit: 1644

of these monocytes into the interstitial spaces, where these monocytes further exacerbate the progressive course of inflammation and fibrosis. The role of these interstitial monocytes in promoting tissue destruction and fibrosis in kidney disease is well established (Rodgers et al., "Tissue monocytes promote myofibroblast accumulation and tubular epithelial cell death in renal fibrosis", *kidney int.* 63, 1338-55 (2003)), thus the mechanism whereby they achieve entry into the interstitial space is a key event in promoting fibrotic kidney disease (see paragraph 3).

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. It is clear that both the '040 publication and applicant administer the same composition comprising the same antibody to the same patient to achieve the same results. The prior art and applicant have suggested different mechanisms. It is acknowledged that applicant now recites and believes in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does applicant provide objective evidence to distinguish the prior art from the claimed invention. It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. *Verdegaal Bros. Inc. V. Union Oil Co. of Calif.*, 814 F.2d 628, 632-33, 2USPQ2d 1051, 1054 (Fed. Cir).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody is not mono-specific antibody recited in the claim. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

14. Claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pat. No. 6,492,325, as is evidence by Dominic Cosgrove Declaration filed in serial No. 10/099,573 on 11/29/04.

The '325 patent teaches and claims a of treating renal fibrosis or crescentic glomerulonephritis (chronic inflammatory diseases), in a patient comprising administering to the patient an effective amount of an $\alpha 1\beta 1$ integrin receptor inhibitor (a blocking agent) (see patented claims 1 and col., 5, lines 40-55 in particular), wherein the $\alpha 1\beta 1$ integrin receptor inhibitor is a blocking agent that binds to the $\alpha 1\beta 1$ integrin receptor binding site on the surface of a kidney cell (col., 5, lines 51-55 in particular), wherein the agent is an antibody, other agents that inhibit the $\alpha 1\beta 1$ integrin receptor by other mechanisms can also be use (see col., 5, lines 58-61 and col., 32 under Example 5 in particular).

While the prior art teachings may be silent as to the "to neutralize the capacity of Collagen XIII to bind to a $\alpha 1\beta 1$ integrin", "characterized by progressive pathogenesis resulting from infiltrating monocytes, lymphocytes, or both", "the blocking agent blocks the interaction of $\alpha 1\beta 1$ integrin on peripheral blood monocytes and/or lymphocytes with collagen XIII on vascular endothelium of chronically inflamed tissue", "where integrin $\alpha 1\beta 1$ -positive interstitial monocyte

Art Unit: 1644

and/or lymphocyte accumulation is observed”, “reducing selective efflux of integrin $\alpha 1\beta 1$ -positive monocytes into the interstitium of chronically inflamed tissues” or reducing the rate of monocyte and/or lymphocyte efflux into the interstitial space of chronically inflamed tissues” per se; the method, the product used in the reference method are the same as the claimed method. Therefore mechanism driving the process of inflammation is considered inherent properties of the referenced method.

Further, as is evidence by Dominic Cosgrove Declaration filed in serial No. 10/099,573 on 11/29/04 that the work describes the existence of an inducible ligand (collagen XIII) for $\alpha 1\beta 1$ integrin on the vascular endothelial cells of inflamed tissue (in this case, the inflamed kidney) that binds to $\alpha 1\beta 1$ integrin-positive peripheral blood monocytes and mediates the transmigration of these monocytes into the interstitial spaces, where these monocytes further exacerbate the progressive course of inflammation and fibrosis. The role of these interstitial monocytes in promoting tissue destruction and fibrosis in kidney disease is well established (Rodgers et al., “Tissue monocytes promote myofibroblast accumulation and tubular epithelial cell death in renal fibrosis”, *kidney int.* 63, 1338-55 (2003)), thus the mechanism whereby they achieve entry into the interstitial space is a key event in promoting fibrotic kidney disease (see paragraph 3).

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. It is clear that both the '040 publication and applicant administer the same composition comprising the same antibody to the same patient to achieve the same results. The prior art and applicant have suggested different mechanisms. It is acknowledged that applicant now recites and believes in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does applicant provide objective evidence to distinguish the prior art from the claimed invention. It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. *Verdegaal Bros. Inc. V. Union Oil Co. of Calif.*, 814 F.2d 628, 632-33, 2USPQ2d 1051, 1054 (Fed. Cir).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody is not mono-specific antibody recited in the claim. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

Art Unit: 1644

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-3, 5-8, 10-13, 15, 17-19, 21-23 and 25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 34-36, 40, 43-45 and 52 of copending Application No. 10/099,573. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to the same methods of treating/limiting renal fibrosis in a patient comprising inhibitor to that inhibits $\alpha 1\beta 1$ integrin receptor. The term "comprising" in instant claim 1 would open up the claim to include TGF- $\beta 1$ agent recited in the '573 application. Further, as is evidence by Dominic Cosgrove Declaration filed in serial No. 10/099,573 on 11/29/04 that the work describes the existence of an inducible ligand (collagen XIII) for $\alpha 1\beta 1$ integrin on the vascular endothelial cells of inflamed tissue (in this case, the inflamed kidney) that binds to $\alpha 1\beta 1$ integrin-positive peripheral blood monocytes and mediates the transmigration of these monocytes into the interstitial spaces, where these monocytes further exacerbate the progressive course of inflammation and fibrosis. The role of these interstitial monocytes in promoting tissue destruction and fibrosis in kidney disease is well established (Rodgers et al., "Tissue monocytes promote myofibroblast accumulation and tubular epithelial cell death in renal fibrosis", kidney int. 63, 1338-55 (2003)), thus the mechanism whereby they achieve entry into the interstitial space is a key event in promoting fibrotic kidney disease (see paragraph 3).


This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. No claim is allowed.

Art Unit: 1644

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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